REMARKS

Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 are present for purposes of prosecution. It appears that these claims have been renumbered as Claims 1 to 22, respectively. However, Applicant is unsure whether the claims should be renumbered at this juncture.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Claim Objections

Claim 5 (old Claim 48) is objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner points out that Claim 48, which depends from Claim 37, contains a broader dosage range for metformin than in the original independent claim

Claim 5 (old Claim 48) has been amended so that the dosage range of metformin is the same as in Claim 1 (old Claim 37).

Claim Rejections - 35 U.S.C. §103

Claims 37, 45 to 54, 58 to 60, 71 to 73, and 75 to 79 are rejected under 35 U.S.C. §103(a) as being unpatentable over Whitcomb (U.S. Patent No. 6,011,049) in view of Bauer et al. (U.S. Patent No. 5,258,185).

The Examiner contends that:

> "Whitcomb teaches a combination of a glitazone antidiabetic and a biguanidine antidiabetic agent for administration in a method of treating diabetes and improving glycemic control (abstract). The reference teaches administration of 0.25-250mg/day of a sulfonylurea and 300-2000 mg/day of a biguanide, citing glyburide and metformin as the preferred sulfonylurea and biguanide, respectively. which overlaps the instantly claimed dosages and dosage ratios (see: col. 4, lines 45-63; claims 1-3, 7-10, 14-16). Regarding claim 54, Whitcomb also teaches that the diabetic patients administered the treatment regimen had fasting plasma glucose levels greater than 200 mg/dL and HbA1c greater than 9% (see: col. 12, Table 2 and col. 16, lines 17-19).
>
> Whitcomb does not teach particle size of glyburide.

Bauer et al. teaches pharmaceutical formulations of glibenclamide (also known as glyburide) rapidly releasing the active substance for the treatment diabetes (abstract). The reference teaches that the preparations having micronized glibenclamide, with a mean particle size of ±5 μm, showed improved drug release and bioavailability (col. 2, lines 17-22). The mean particle size of ±5 μm overlaps the instantly claimed particle size range of 2-60 μm. Bauer et al. does not teach co-administration with metformin.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use glyburide with a particle size of ±5 μm in the method of Whitcomb. The skilled artisan would have been motivated to use glyburide with a particle size of ±5 μm, having been taught by the prior art (Bauer et al.) that it has improved drug release and bioavailability. The person of ordinary skill in the art would have had a reasonable expectation of success in treating a diabetic with a combination of glyburide and metformin, having been taught by the prior art (Whitcomb) that it is known that administration of the two compositions together in a treatment regimen results in improved glycemic control. Therefore, the invention as a whole would have been prima facie obvious."

U.S. Patent No. 6,011,049 to Whitcomb is based on U.S. Application No. 09/189,132 filed November 9, 1998, which is a continuation-in-part of Application No. 08/970,057 filed November 13, 1997 which issued as U.S. Patent No. 5,859,037 to Whitcomb, which is based on Provisional Application No. 60/039,224 filed February 19, 1997.

The Examiner has cited U.S. Patent No. 6,011,049 to Whitcomb rejecting the claims of the subject application.

U.S. Patent No. 6,011,049 to Whitcomb discloses a combination of a glitazone antidiabetic agent and a biguanide such as metformin and optionally a sulfonyl urea antidiabetic agent such as glyburide.

The parent U.S. Patent No. 5,859,037 to Whitcomb based on Application No. 970,057 filed November 13, 1997 discloses a combination of a sulfonyl urea antidiabetic agent and a glitazone antidiabetic agent. There is no disclosure or suggestion in the '037 patent of a combination which includes a biguanide such as metformin.

The Provisional Application No. 60/038,224 filed February 19, 1997 does not include a disclosure of a combination which includes a biguanide such as metformin.

In view of the above, the effective date of U.S. Patent No. 6,011,049 as a reference for combinations containing a sulfonyl urea such as glyburide and a biguanide such as metformin is November 9, 1998.

Applicant has previously submitted a Declaration of Prior Invention of Beth Anne Piper in the United States to Overcome Cited U.S. Patent No. 6,303,146 (37 C.F.R. §1.131) (copy enclosed without previously filed exhibits) which has a priority date or effective date as a reference of July 15, 1998 as well as a Declaration of Burton Rodney to show due diligence to a constructive reduction to practice (copy enclosed). By way of such Declarations, Applicant established conception prior to July 15, 1998 and with due diligence an actual reduction to practice of the invention claimed on or about November 24, 1999, and exercised due diligence in a constructive reduction to practice with the filing of the subject application on December 14, 1999.

Thus, as seen from the Piper Declaration, the inventor established conception prior to July 15, 1998 and a reduction to practice with due diligence thereafter. Accordingly, it will be apparent that the inventor has effectively removed U.S. Patent No. 6,011,049 to Whitcomb as a reference against the subject application.

U.S. Patent No. 5,258,185 to Bauer et al. discloses in Col. 2, lines 17 to 20,

> "microionized, i.e. finely comminuted, glibenclamide (mean particle size ±5 μm) showed an improved drug release and bioavailability above all in the presence of tensides . . ."

Glibenclamide and glyburide are synonymous.

There is no disclosure or suggestion in Bauer et al. of a method of treating diabetes in a drug naïve patient employing a low dose of a combination of metformin and glyburide. Bauer et al. discloses formulations containing glyburide but not metformin. Accordingly, it is clear that Applicant's invention as claimed is patentable over Bauer et al.

The Examiner also cites Barelli et al. U.S. Patent No. 6,922,769 as disclosing a combination of metformin and glyburide (equivalent to Whitcomb) and U.S. Patent No. 3,979,520 as disclosing glyburide having special particle sizes (equivalent to Bauer et al.).

Barelli et al. U.S. Patent No. 5,922,769 discloses tablets containing glibenclamide and metformin hydrochloride for treating type II diabetes. However, there is no disclosure or suggestion in Barelli et al. of glibenclamide having a special particle size distribution to improve its absorbability and efficacy characteristics. In addition, Barelli et al. discloses use of glyburide (15 mg) in a ratio to metformin of 1:100 or 1500 mg metformin. There is no disclosure or suggestion in Barelli et al. of use of low dose metformin (160-170 mg daily) as claimed in Applicant's Claim 37 (now Claim 1).

Accordingly, it is clear that Applicant's invention as claimed which requires low dose metformin and glyburide (glibenclamide) having the special particle size distribution as claimed, is patentable over Barelli et al.

Rothe et al. U.S. Patent No. 3,979,520 discloses a rapidly resorbable glibenclamide characterized by having a particle surface area of at least 3 m^2/g, preferably 5 to 10 m^2/g.

As indicated hereinbefore and on page 6 starting at line 9 of Applicant's Specification, the glyburide having the particle size distribution claimed herein has a powder surface area in the range of about 1.7 to 2.2 m^2/g. Thus, Rothe et al. disclose glyburide which is very different in powder surface area, and therefore particle size distribution, from that claimed herein.

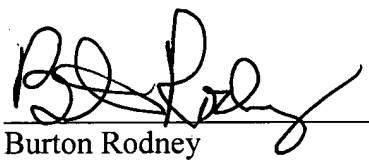
Column 1 of Rothe discloses commercial "glibenclamide...in the form of particles with a surface area of 1-2 m^2/g". However, Rothe et al. do not disclose or suggest the particle size distribution of such glibenclamide. Glyburide having a surface area of 1-2 m^2/g could have practically hundreds, if not thousands or even more particle size distributions. Accordingly, one skilled in the art reading Rothe et al. would not have the slightest inkling as to the particle size distribution of the glibenclamide mentioned in Column 1 of Rothe et al.

In view of the foregoing it is clear that Applicant's invention as claimed is patentable over Rothe et al. (U.S. Patent No. 3,979,520).

Applicant's method as claimed is also patentable over a combination of Barelli et al. and Rothe et al. As indicated, Barelli et al. does not disclose or suggest use of low dose metformin (160 to 750 mg daily) but only discloses use of 1500 mg metformin daily. Barelli et al. is devoid of Applicant's inventive concept of use of a combination of <u>low dose</u> metformin and specially size glyburide in first line treatment of drug naïve patients. Rothe et al. does not add anything to Barelli et al. which would make Applicant's method as claimed obvious since Rothe et al. does not disclose or suggest the specially sized glyburide required by Applicant. Even if Barelli et al. is taken with Bauer et al., the resulting combination would not make Applicant's method obvious since neither reference discloses or suggests use of low dose metformin.

In view of the foregoing, it is submitted that Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 (new Claims 1 to 22) are patentable over the cited art and are in condition for allowance.

Respectfully submitted,



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